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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,147	KINDL ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-20* is/are pending in the application.

4a) Of the above claim(s) *5,7 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP00/09912.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 15, 2007 has been entered.

The amendment filed August 16, 2007, amending claims 1-3, 6, 9 and 11-14 and canceling claim 4, has been entered. The amendment is supported by the original specification and original claims. Therefore, the amendments contain no new matter.

Claims 1-3 and 5-20 are pending. Claims 5, 7 and 15-20 are withdrawn. Claims 1-3, 6 and 8-14 are under consideration.

Response to Arguments/Amendments

Applicant's amendment and arguments filed August 16, 2007, have been fully considered and are deemed to be persuasive to overcome some of the rejections/objections previously applied, as detailed below.

Claim Objections

Withdrawn Objections

In view of the cancellation of claim 4, the objections to claim 4 has been **withdrawn.**

In view of the amendments of claims 1-3, 6, 8 and 11-14, the objections to claims 1-3, 6, 8 and 11-14 have been **withdrawn.**

New Objection

Claim 2 is objected to because of the following informalities: claim 2 recites the phrase "protein is selected from the fatty acid desaturase(s)". It appears that the article "the" is unnecessary. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Withdrawn Rejections

In view of the amendment of claims 1-3 and cancellation of claim 4, the rejections of claims 1-4 and claims 6 and 8-14 depending therefrom under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been **withdrawn**.

New Rejection

Claim 1 and claims 2-3, 6 and 8-14 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "nucleic acid sequence encoding a fatty acid or lipid metabolism". The metes and bounds of this phrase are not clear to the Examiner. It is not clear to the Examiner how a nucleic acid can encode for a fatty acid metabolism or a lipid metabolism, since nucleic acids only encode polypeptides. The phrase does not make any scientific sense. Examiner requests clarification of the above phrase.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1-3, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2, and vectors and host cells comprising said polynucleotide. However, the polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2 was not described in the application as originally filed nor in any of its parent applications. The specification as filed contains disclosure of only polynucleotides encoding a fusion protein comprising a polypeptide having at least 50, 60, 70 or 80% homology to SEQ ID NO:2. Therefore, the claims contain new matter.

Given this lack of description of the polynucleotide encoding a fusion protein comprising a polypeptide having at least 95% homology to SEQ ID NO:2 and vectors and host cells comprising said polynucleotide in the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-3, 6 and 8-14 at the time of filing of the instant application.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that a polypeptide having at least 95% homology with SEQ ID NO:2 is inherently described in homologies of at least 50, 60, 70 and 80% homologies with SEQ DI NO:2 and would be readily recognized by an individual having ordinary skill in the art. Examiner respectfully disagrees. The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement

of 35 U.S.C. 112, first paragraph (see MPEP 2163.05 – II. Narrowing or subgeneric claim). In the instant case, the broader described range (a polypeptide having at least 50, 60, 70 and 80% homologies with SEQ ID NO:2) does not describe the narrower claimed range (a polypeptide having at least 95% homology to SEQ ID NO:2) because there was no disclosure of either the range itself or of a sufficient number of species to establish entitlement to the claimed narrower range.

Hence the rejection is maintained.

Claims 1-3, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a polynucleotide encoding a Δ-4 desaturase and (1) a polynucleotide encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2 or (2) a nucleic acid sequence of SEQ ID NO:1.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." " In this case, the examiner has broadly interpreted "a nucleic acid sequence of SEQ ID NO:1" to encompass a fragment of as few as 2 contiguous nucleic acids of SEQ ID NO:1. Further, since the function of the protein is not recited, the claims encompass any polynucleotides encoding a fusion protein comprising a polynucleotide encoding a Δ-4 desaturase and

(1) a polynucleotide encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2 or (2) a polynucleotide comprising as few as two contiguous nucleic acids SEQ ID NO:1, wherein the encoded polypeptide of (1) or (2) has any function or no function.

In *University of Calfornia v. Eli Lilly & Co.,* 43 USPQZd 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, (or) chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Therefore, in the instant case regarding claim 1(a), the claims are drawn to a polynucleotide comprising any structure. The specification only describes a

polynucleotide encoding a fusion protein, wherein said polynucleotide comprises the nucleic acid sequence of SEQ ID NO:1 and a desaturase. While MPEP 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In view of the widely variant species encompassed by the genus, this one example is not enough and does not constitute a representative number of species to describe the whole genus of any or all variants, recombinant and mutants of any or all polynucleotide isolated from any or all source, including any or all variants, recombinants and mutants thereof, and there is no evidence on the record of the relationship between the structure of SEQ ID NO:1 and the structure of any or all recombinant, variant and mutant of any or all polynucleotides thereof. Therefore, the specification fails to describe a representative species of the genus comprising any or all polypeptides having serine protease activity, including any or all variants, recombinants and mutants thereof.

The claims also encompass polynucleotides encoding a fusion protein comprising polypeptides having at least 95% sequence identity to SEQ ID NO:2 and Δ-4 desaturase, wherein said polypeptide has any activity or no activity and the resulting fusion protein has any activity or no activity. Therefore, these claims are drawn to a genus polynucleotides encoding a fusion protein comprising Δ-4 desaturase and a polypeptide having 95% amino acid sequence identity with SEQ ID NO:2, wherein said

fusion protein has any function or no function. There is no disclosure of any particular structure to function/activity relationship in the disclosed species.

The claims are drawn to many functionally unrelated polynucleotides are encompassed within the scope of these clams, including partial sequences. The genus of these polynucleotides comprise a large variable genus with the potentiality of encompassing many different polynucleotides encoding fusion proteins having different activity or no activity. The specification discloses only a single species of the claimed genus, a polynucleotide encoding a fusion protein comprising a polypeptide of SEQ ID NO:2 and a Δ-4 desaturase, wherein said desaturase continues to have Δ-4 desaturase activity and SEQ ID NO:2 targets said desaturase to lipid bodies. The specification fails to describe additional representative species of the polynucleotides by any identifying characteristics or properties of the encoded polypeptides, for which no predictability of function is apparent. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that since applicants have amended the claims to recite "95%", the claims meet the written description requirement. Examiner respectfully disagrees. The claims remain to be drawn to polynucleotides having 95% sequence

identity to SEQ ID NO:2, wherein said polynucleotide encodes a fusion proteins having any or no or unknown activity. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, **by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.** A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genus of the claims includes species which are widely variant in function and structure. The genus of the claims is functionally/structurally diverse as it encompasses polynucleotides encoding polypeptides with LBLOX activity, polypeptides that target

proteins to lipid bodies and any polypeptides which lack such activity and those with no activity.

Applicants also argue that the specification fully complies with the written description requirement because it allows one of ordinary skill in the art to practice the invention, such as the specific example of a polynucleotide encoding a fusion protein comprising the polypeptide of SEQ ID NO:2 and a desaturase, summary information for the function of lipids and fatty acids and general molecular biology techniques. Examiner respectfully disagrees. The claims are not limited to a polynucleotide encoding a fusion comprising the polypeptide of SEQ ID NO:2, but the claims encompass any polynucleotides encoding a fusion protein comprising a polynucleotide encoding a Δ-4 desaturase and (1) a polynucleotide encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2 or (2) a polynucleotide comprising as few as two contiguous nucleic acids SEQ ID NO:1, wherein the encoded polypeptide of (1) or (2) has any function or no function. As discussed above, in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, **by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Thus, when there is substantial variation within the genus, one must describe a**

sufficient variety of species to reflect the variation within the genus. In the instant case the claimed genus of the claims includes species which are widely variant in function and structure.

Hence the rejection is maintained.

Claims 1-3, 6 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fusion protein comprising a polypeptide of SEQ ID NO:2 and a Δ-4 desaturase, wherein said desaturase continues to have Δ-4 desaturase activity and SEQ ID NO:2 targets said desaturase to lipid bodies, does not reasonably provide enablement for a polynucleotide comprising a desaturase and a polynucleotide having unknown structure/function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a polynucleotide encoding a Δ-4 desaturase and (1) a polynucleotide

encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2 or (2) a nucleic acid sequence of SEQ ID NO:1.

It is noted that MPEP 2111.01 states that "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." " In this case, the examiner has broadly interpreted "a nucleic acid sequence of SEQ ID NO:1" to encompass a fragment of as few as 2 contiguous nucleic acids of SEQ ID NO:1. Further, since the function of the protein is not recited, the claims encompass any polynucleotides encoding a fusion protein comprising a polynucleotide encoding a Δ-4 desaturase and (1) a polynucleotide encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2 or (2) a polynucleotide comprising as few as two contiguous nucleic acids SEQ ID NO:1, wherein the encoded polypeptide of (1) or (2) has any function or no function. Therefore, the claims are drawn to a polynucleotide encoding a fusion protein comprising a desaturase and a polypeptide of unknown structure and/or function.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides comprising, variants and mutants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is

limited to a polynucleotide encoding a fusion protein comprising a specific fatty acid/lipid metabolism enzymes such as Δ-4 desaturase and the SEQ ID NO:2.

It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides. The specification provides no guidance with regard to the making of variants and mutants of SEQ ID NO:2 or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of polynucleotides of SEQ ID NO:1 because the specification does not establish: (A) regions of the encoded protein structure which may be modified without affecting LBLOX activity or its ability to target foreign proteins

to lipid bodies; (B) the general tolerance of LBLOX to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful; (E) the specification is also silent regarding the final activity of fusion proteins of SEQ ID NO:2.

The claims also broadly encompass not only polynucleotides encoding LBLOX or fragments of LBLOX having ability to target foreign proteins to lipid bodies and enzymes of fatty acid/lipid metabolism, but polynucleotides encoding polypeptides having any function or having no function. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The specification does not teach how to make variants of polynucleotides of SEQ ID NO:1 or polynucleotides of fatty acid/lipid metabolism encoding polypeptides having any function. The function of a polypeptide cannot be predicted from its structure and the specification does not teach how to use polypeptides having any function or having no activity. The quantity of experimentation in this area is extremely large since there is significant variability in the activity of the polynucleotides in the claims. It would require significant study to identify the actual function of the encoded polypeptides and identifying a use for the encoded polypeptide would be an inventive, unpredictable and difficult undertaking. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotide comprising variants and mutants of any polynucleotides of fatty acid/lipid metabolism and any mutants and variants of SEQ ID NO:1 encoding polypeptides having any structure and any function. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variants or mutants of SEQ ID NO:1 and polynucleotides of fatty acid/lipid metabolism having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that one of ordinary skill in the art would be able to create the working examples and the guidance in making such examples are minimal and routine. Examiner respectfully disagrees. The specification discloses only the a

polynucleotide encoding a fusion protein comprising a specific fatty acid/lipid metabolism enzymes such as Δ-4 desaturase and the SEQ ID NO:2, wherein the LBLOX of SEQ ID NO:2 targets Δ-4 desaturase to lipid bodies. However, the speciation fails to provide any information as to (1) specific substrates associated with polynucleotides encoding SEQ ID NO:2 and its variants, (2) structural elements required in a polypeptide in targeting foreign polypeptides to lipid bodies, or (3) which are the structural elements in the polypeptide of SEQ ID NO:2 that are essential in targeting foreign polypeptides to lipid bodies. No correlation between structure and function of polypeptides that target foreign polypeptides to lipid bodies has been presented. There is no information or guidance as to which amino acid residues in the polypeptides encoded by SEQ ID NO:2 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 in a fusion polypeptide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Applicants also argue that one of ordinary skill in the art would be able to determine to a sufficient degree in making amino acid substitutuions, without requiring undue experimentation. Examiner respectfully disagrees. Claim 1 a) is drawn to "a nucleic acid sequence of SEQ ID NO:1", which encompasses a fragment of as few as 2 contiguous nucleic acids of SEQ ID NO:1. Therefore, the claims are drawn to a polynucleotide encoding a fusion protein encoding a desaturase and a polypeptide encoded by any fragment of SEQ ID NO:1, as little as two nucleic acids. As discussed

above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. While the art may teach in general the structure of the LBLOX of SEQ ID NO:2 conserved amino acid sequences, X-ray crystal structure and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art.

Applicants also argue that there is no undue experimentation and the presence of inoperative embodiment within the scope of a claim does not necessarily render a claim non-enabled. Examiner respectfully disagrees. There is no information or guidance as to which amino acid residues in the polypeptides encoded by SEQ ID NO:2 can be modified and which ones are to be conserved to create a polypeptide displaying the same activity as that of the polypeptides of SEQ ID NO:2 in a fusion polypeptide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. Since the scope of the claims require an undue experimentation to make and use the claimed polynucleotides, the claims are also not commensurate with the enablement provided by the disclosure with regard to inoperative embodiments encompassed by the claims. Although the presence of inoperative embodiments within the scope of the claims does not necessarily render a claim non-enabled, the standard is whether a skilled person could determine which

embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The scope of the claims are not enabled when undue experimentation is involved in determining those embodiments that are operable. In the instant case, the claims read on significant numbers of inoperative embodiments, rendering the claims non-enabled, since the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

Applicants also argue that since computational techniques were available to arrive at the claimed sequences, one of ordinary skill in the art would have ready knowledge of and predictability of activity after amino acid substitutions. Examiner respectfully disagrees. First, the claims are drawn to polynucleotides encoding polypeptide having any structure and/or unknown activity or no activity. The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides. Second, while a skilled artisan can produce variants of the polypeptide of SEQ ID NO: 2 having the recited structural characteristics

using well-known and widely used techniques in the art, the amount of experimentation required is not routine nor predictable to the fact that the claims encompass an extremely large number of polynucleotides comprising, variants and mutants broadly encompassed by the claims.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hohne et al,, Ohlrogge et al. and Yamamoto et al.

Claims 1-3, 6 and 8-14 are drawn to a polynucleotide encoding a fusion protein comprising a Δ-4 desaturase and SEQ ID NO:2, vector comprising said polynucleotide and *S. cerevisiae* comprising said polynucleotide.

Hohne et al. (form PTO-1449 – Eur. J. Biochem. 241, 1996: 6-11 and form PTO-892 - NCBI Accession CAA63483.1) discloses a polynucleotide encoding a lipid body lipoxygenase (LBLOX), wherein amino acid at positions 1-244 is 100% identical to SEQ ID NO:2 (page 2, 3rd paragraph and see Sequence Alignment – cited previously on form PTO-892). Hohne et al. teaches that LBLOX is synthesized and transported to lipid

bodies at the beginning of lipid body mobilization, during which fatty acids/lipids are metabolized (pages 6 and 8-9). Hohne et al. also teaches that the N-terminal region of LBLOX may represent a targeting sequence and may be responsible for the attachment of LBLOX to the lipid body surface (page 10). Hohne et al. also teaches that a comparison between the molecular mass of the *in vitro* and *in vivo* form of LBLOX did not indicate significant proteolytic processing and LBLOX is only slightly higher in mass than its cytosolic form, suggesting that the N-terminal region of LBLOX contains a recognition site for lipid bodies (page 10). It is well within the skill available in the art to identify sequences in the N-terminal region of LBLOX that target LBLOX to lipid bodies and attach any protein to such sequences, in order to target the protein of interest to lipid bodies. Further, the claims do not recite that the fusion partner to the desaturase consist of SEQ ID NO:2, therefore, full length LBLOX of Hohne et al. or its N-terminal region comprising SEQ ID NO:2, are encompassed by scope of the claims.

The difference between the reference of Hohne et al. and the instant claims is that the reference of Hohne et al. does not teach a polynucleotide encoding a fusion protein comprising a Δ-4 desaturase fused to LBLOX, vectors comprising said polynucleotide or microorganism comprising said polynucleotide.

Ohlrogge et al. (form PTO-892 - Oils-Fats-Lipids 1995) teaches a polynucleotide encoding a Δ-4 desaturase, which is an enzyme of fatty acid/lipid metabolism (abstract).

Yamamoto et al. (form PTO-892 – U.S. Patent No. 5,506,120) teaches a polynucleotide encoding a fusion protein, linking proteins via a regulatory signal, vectors

comprising said polynucleotide and a *Saccharomyces cerevisiae* comprising said polynucleotide (abstract and Columns 5-14).

Therefore, combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising the full length LBLOX of Hohne et al. and a target protein of interest, such as enzymes involved in fatty acid/lipid metabolism. Alternatively, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was to identify sequences that target LBOX to lipid bodies in order to target other proteins of interest, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies. Upon identifying the targeting sequences, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising said sequences and a fatty acid/lipid metabolism enzyme of interest, such as the desaturase of Ohlrogge et al., using the method taught by Yamamoto et al. One having ordinary skill in the art would have been motivated to use full length LBLOX or to identify sequences that target LBLOX to lipid bodies, in order to use them to target other proteins, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies, and make a polynucleotide encoding a fusion comprising said sequence and desaturase, thereby directing the enzyme to the site where its activity is desired. One of ordinary skill in the art would have had a reasonable expectation of success in making the polynucleotide since making polynucleotides encoding fusion proteins is well known in the art, as taught by Yamamoto et al. One of ordinary skill in the art would have had a

reasonable expectation of success in making a fusion protein comprising the full length LBLOX to target protein to lipid bodies since Hohne et al. teaches that the full length LBLOX is targeted to lipid bodies. Similarly, one of ordinary skill in the art would have had a reasonable expectation of success in identifying N-terminal sequences of LBLOX of Hohne et al. that target proteins to lipid bodies and making a fusion protein comprising such N-terminal sequences to target protein to lipid bodies since Hohne et al. teaches that the N-terminal region of the LBLOX may be responsible for targeting proteins to lipid bodies.

Therefore, Hohne et al., Ohlrogge et al. and Yamamoto et al. in combination render claims 1-3, 6, 8-9 and 10-14 *prima facie* obvious to those skilled in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that Hohne et al. fails to teach or suggest the targeting of fusion proteins to liposomes, fails to teach anything in the technical field of fusion proteins; the reference is related to the physiological characterization of a lipoxygenase from cucumber, and therefore, one of ordinary skill in the art would not be motivated to combine or modify said cited art. Examiner respectfully disagrees. The rejection is an obviousness rejection, not an anticipation rejection. Therefore, Hohne et al. does not have to teach all limitations of the claimed invention. What Hohne et al. discloses is that the N-terminal portion of CSLBLOX is the targeting sequence toward lipid bodies. With this teaching at hand, one having ordinary skill in the art would have been motivated to

use it as a targeting sequence. The teachings of fusion proteins is provided by Yamamoto et al.

Applicants also argue that Ohlrogge et al. discloses only a polynucleotide encoding a desaturase and its function in fatty acid biosynthesis and fails to teach or suggest about targeting sequences or fusion proteins. Again, the rejection is an obviousness rejection, not an anticipation rejection. Therefore, Ohlrogge et al. does not have to teach targeting sequences or fusion proteins. The reference of Ohlrogge et al. is relied upon for its teaching of polynucleotide encoding a Δ-4 desaturase, which is an enzyme of fatty acid/lipid metabolism (abstract). Upon combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising the LBLOX of Hohne et al. and the desaturase of Ohlorogge et al., in order to target other proteins of interest, such as enzymes involved in fatty acid/lipid metabolism such as a desaturase, to lipid bodies.

Applicants also argue that Yamamoto et al. fails to teach or suggest the fusion process for combining LBLOX and desaturase. Again, the rejection is an obviousness rejection, not an anticipation rejection. Therefore, Yamamoto et al. does not have to teach a process for combining LBLOX and desaturase. Further, the claims are drawn to a polynucleotide and not a method of targeting proteins, and the claims do not recite targeting proteins to liposomes or lipid bodies. Also, the reference of Yamamoto et al. is relied upon for its teaching of teaches a polynucleotide encoding a fusion protein, linking proteins via a regulatory signal, vectors comprising said polynucleotide and a

Saccharomyces cerevisiae comprising said polynucleotide (abstract and Columns 5-14). Upon Combining the teachings of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was length made to make a polynucleotide encoding a fusion protein comprising the LBLOX of Hohne et al. and a target protein of interest, such as enzymes involved in fatty acid/lipid metabolism.

Applicants also argue that there is no motivation to combine the references, without offering any arguments as to why there is not motivation to combine the references. As discussed in the rejection, one having ordinary skill in the art would have been motivated to use full length LBLOX or to identify sequences that target LBLOX to lipid bodies, in order to use them to target other proteins, such as enzymes involved in fatty acid/lipid metabolism, to lipid bodies, and make a polynucleotide encoding a fusion comprising said sequence and desaturase, thereby directing the enzyme to the site where its activity is desired

Hence the rejection is maintained.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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Yong D. Pak
Patent Examiner 1652